

Remarks/Arguments

Claims 58, 69, 61-66, and 81-96 are pending in this application. Claims 62-64, 66, 90-92, and 94 are withdrawn from consideration, and claims 58, 59, 61, 65, 81-89, 93, 95, and 96 are rejected on various grounds.

Withdrawn Objections/Rejections

Applicants appreciate the withdrawal of the objection to claim 87 and the rejections under 35 U.S.C. § 112, second paragraph.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 58, 59, 61, 65, 81-89, 93, 95, and 96 (all claims under examination) remain to be rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Kim et al. (WO 98/11436, March 19, 1998) and Siuzdak, G. (Mass Spectrometry for Biotechnology, New York: Academic Press, 1996, pages 119-126).

The rejections are based on the premise that Kim et al. teaches all elements of independent claims 58 and 86, with the exception of using mass spectrometry, which element is supplied by Siuzdak et al. In addition, the Examiner finds that the specific recitations of dependent claims are either taught by or obvious over Kim et al, noting that when “the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).”

Applicants appreciate the Examiner’s thorough analysis of the cited references, but submit that the references are improperly combined, and respectfully disagree with the way the cited combination of references is applied to the claims, and the conclusions drawn from the analysis.

A. *A prima facie case of obviousness has not been established*

The U.S. Court of Appeals for the Federal Circuit has held that

[t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness . . . It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The case law is also clear that the motivation to support a combination of references in a Section 103 rejection must withstand scrutiny.

In In re Rouffet, 149 F.3d 1350; 47 USPQ2d 1453 (Fed. Cir. 1998) , the CAFC reaffirmed that a suggestion to combine known elements present in various pieces of prior art is critical for establishing a *prima facie* case of obviousness. The CAFC observed that:

“[V]irtually all [inventions] are combinations of old elements.” Environmental Designs, Ltd. V. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2s 1573, 1579-80, 219 U.S.P.Q. 8, 12 (Fed. Cir. 1983) (“Most, if not all, inventions are combinations and mostly of old elements.”). Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such approach would be “an illogical and inappropriate process by which to determine patentability.” Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).

In re Rouffet, 149 F.3d at 1357 47 U.S.P.Q.2d at 1457

The requirement that an examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. The motivation to modify a reference can come from (1) the nature of the problem to be solved, (2) the teachings of the prior art itself, or (3) the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d at 1358; 47 U.S.P.Q.2d at 1458.

In the present case, the motivation to combine Kim et al. and Siuzdak et al. does not come from any of the three recognized sources, as shown by the analysis of the two independent claims, claims 58 and 86.

Initially, Applicants note that the Examiner's motivation analysis focuses on the question whether one skilled in the art would have been motivated to combine the teachings of Kim et al. with Siuzdak et al. to detect a single target protein-compound conjugate by mass spectrometry. This approach, which is apparent from the analysis throughout the Office Action, and in particular at pages 8-11, is incorrect. The problem faced by the present inventors, which is addressed by the claimed invention, is the detection of a particular target protein-compound conjugate, and identification of the compound present in such conjugate in a mixture.

1. The motivation to combine Kim et al. and Siuzdak et al. does not derive from the nature of the problem to be solved

For the invention described in *Claim 58*, the relevant problem to be solved is the detection of the most abundant target protein-compound conjugate in a mixture of target protein-compound conjugates, and the determination of the identity of the compound present in the most abundant conjugate, which will be the compound having the greatest relative affinity for the target protein of the compounds present in the mixture assayed. This problem is complex, requiring the detection of the most abundant target protein-ligand conjugate from among a potentially large number of conjugates, in the presence of the other conjugates, and, in addition, determination of the identity of the compound which is present in the most abundant conjugate.

Mass spectrometry would not have been the method of choice for addressing this problem, since one skilled in the art would have anticipated significant difficulties arising from the presence of a plurality of conjugates, and the corresponding monomers (unbound target protein and unbound ligand candidates), and from the fact that the molecular weights of the conjugates present in the mixture are likely to be close to each other, and therefore difficult to distinguish. The skilled artisan would have been more inclined to eliminate all but one conjugate, which can then be detected, for example, by antibody-based detection methods, as Kim et al. appears to suggest.

For the invention described in *Claim 86*, the problem to be solved is to detect the most abundant protein-compound conjugate formed in a mixture containing the target protein, at least two compounds that are capable of forming a conjugate with the target protein through disulfide bond formation and a reducing agent. Again, the problem is to detect a particular (most abundant) conjugate in a mixture, for which mass spectrometry would not have been a method of choice for reasons discussed above. More likely, one skilled in the art would have contemplated eliminating all but the most abundant conjugate, for example, by adjustment of the redox conditions, as suggested by Kim et al. (see, e.g. Example 1).

2. The motivation to combine Kim et al. and Siuzdak et al. does not derive from the teachings of the prior art itself

Kim et al. states: “The result of these interactions [i.e. interactions between target molecules and potential ligands] is a mixture, which may include any or all of the following: untethered potential ligands, untethered target molecules, tethered potential ligands, untethered ligands and tethered ligands. Specific binding of a target molecule and a potential ligand tethered thereto is determined (and, thus, a ligand of the target molecule is identified), using known methods.” (Page 14, lines 2-6.) Similarly, at page 21, lines 6-9, Kim et al. notes: “Once specific binding of a ligand in a library of potential ligands with the target molecule has occurred, detection of the resulting complex (ligand bound to target molecule) can be carried out using known methods.” There is no mention of mass spectrometry as a detection method anywhere in Kim et al.

Siuzdak et al. does not provide a motivation for the purported combination either. Siuzdak et al. teach the use of electrospray ionization mass spectrometry for studying noncovalent binding between an antibody and its antigen. In the last sentence, the authors note, without any evidence and without the citation of any reference, that “[e]lectrospray ionization mass spectrometry has also demonstrated its potential in the analysis of noncovalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction.” There is no disclosure, suggestion or hint in Siuzdak et al. that mass spectrometry could be used to detect and a particular complex between a target protein and

an unknown ligand of the protein in a mixture, comprising a plurality of related molecules, and to identify the ligand present in the mixture.

3. The motivation to combine Kim et al. and Siuzdak et al. does not derive from the knowledge of persons of ordinary skill in the art

The Examiner cited no evidence that would indicate that the motivation to combine Kim et al. and Siuzdak et al. would be provided by the knowledge of persons of ordinary skill in the art as of the effective filing date of the present application.

In lack of motivation to combine, the combination of Kim et al. and Siuzdak et al. is improper, and, as a result, a *prima facie* case of obviousness has not been established.

- B. *Even if a prima facie case of obviousness had been established, the cited combination of references would not render obvious the claimed invention*

Since the Examiner has not established a *prima facie* case of obviousness, the burden of rebutting the rejection has not shifted to the Appellants. Nonetheless, it is submitted that, even if the cited references could be properly combined, their combination would not establish that at the effective filing date of the present application one skilled in the art could have arrived at the claimed invention with a reasonable expectation of success.

Despite a general statement that target molecule-ligand complexes (conjugates) can be detected by “general methods,” the only specific teaching in Kim et al. for the detection of the “most abundant” conjugate, as discussed by the Examiner, is provided in Example 1, when glutathione is used in different ratios to identify the ligand which binds the target with the highest affinity. As the Examiner correctly notes, following this method, “only the non-oligomeric organic ligands with the ‘highest affinity’ will remain resistant to the highest ‘ratios’ of reduced/oxidized glutathione. Consequently, . . . at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the ‘non-oligomeric organic compound having the greatest relative affinity’ would be the only one that exists at the higher ratios [ratios] or [of] reduced/oxidized glutathione.”

In discussing Siudzak et al., the Examiner heavily relies on the excerpt relating to catalytic antibodies. When catalytic antibodies were first described, enzymes and the essence of

catalysis were being probed. One theory was that enzymes worked by stabilizing the transition states of the reactants. If this were so, then it should have been possible to generate catalytic antibodies by creating antibodies using transition state analogs, as haptens. As it turns out, the theory about the stabilization of transition states was correct, and many catalytic antibodies were developed.

Siuzdak focuses on an esterase reaction of a catalytic antibody using mass spectrometry (Figure 6.5). The goal discussed by Siuzdak was discerning the steps involved in the catalysis, including formation of an acyl-antibody intermediate, which was postulated but not proven until the experiments (see page 125). This is a detailed examination of a single reaction between the antibody as the enzyme and the hapten as the known substrate.

Combining the teaching of Kim et al. with the use of mass spectrometry, as taught by Siuzdak et al., would at best result only in a method in which a single “target protein-compound conjugate,” which is not present in a mixture, is detected by mass spectrometry. Since the language of independent claims 58 and 86 requires that a mixture of target protein-compound conjugates be subjected to mass spectrometry analysis, the combination of Kim et al. and Siuzdak et al. does not result in the method claimed in the present application. This difference is very meaningful since, as discussed above, the presence of a plurality of target protein-ligand conjugates, as well as the corresponding monomers poses special problems for mass spectrometry analysis, which are not addressed by Siuzdak et al., or the combination of Kim et al. and Siuzdak et al.

In conclusion, a person skilled in the art at the time the present invention was made would not have had a reasonable expectation that by applying the teachings of Siuzdak et al. about the technique of electrospray ionization mass spectrometry to the teaching of a tethering approach by Kim et al. the most abundant target protein-compound conjugate could be detected in a mixture (claims 58 and 86), and the identity of the non-oligomeric organic compound present in the conjugate identified (claim 58). It is only with hindsight reconstruction of the invention, using the disclosure of the present application, that the Examiner could have been led to the finding of obviousness over the cited combination of references. It is, however, well established that it is impermissible to use the claimed invention as an instruction manual or

"template" to piece together the teachings of prior art so that the claimed invention is rendered obvious.

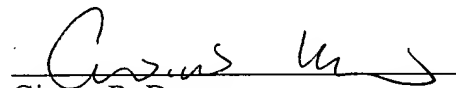
Since the two independent claims are unobvious over the cited combination of references, the dependent claims, carrying the limitations of the claims from which they depend, do not need to exhibit independent indicia of patentability. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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